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Anticonvulsant Step Therapy Criteria with Medical Diagnoses Option*

* Medical diagnoses are required for implementation of this option.

Brand	Generic	Dosage Forms
Keppra®	levetiracetam	tablets ^a , oral solution ^a , injection
Keppra XR™	levetiracetam	extended-release tablets
Lamictal®	lamotrigine	tablets ^a , chewable dispersible tablets ^a , starter kits ^a
Lamictal® ODT™	lamotrigine	orally disintegrating tablets
Lamictal® XR™	lamotrigine	extended-release tablets
Lyrica®	pregabalin	capsules
Topamax®	topiramate	tablets ^a , sprinkle capsules ^a
Trileptal®	oxcarbazepine	tablets ^a , oral suspension ^a
Vimpat™	lacosamide	tablets, injection

a – currently available as generic

PROGRAM OBJECTIVES

The intent of the Anticonvulsant Step Therapy criteria for the brand products Keppra (levetiracetam), Keppra XR (levetiracetam ER), Lamictal (lamotrigine), Lamictal ODT (lamotrigine orally disintegrating), Lamictal XR (lamotrigine ER), Lyrica (pregabalin), Topamax (topiramate), Trileptal (oxcarbazepine), and Vimpat (lacosamide) is to accommodate their use for the treatment of seizure disorders while encouraging use of other generic medications first for their other labeled and accepted unlabeled indications. If the Medical Diagnoses option is implemented, these agents will pay automatically for patients with a documented seizure disorder. Also, patients who are currently receiving therapy with one of the target brand anticonvulsants will be allowed continuation of therapy without meeting the above edit requirements if a claim for the identical anticonvulsant is identified within 90 days prior to the new claim. The criteria for Lyrica encourage its use for neuropathic pain after trial and failure of amitriptyline, nortriptyline, imipramine, desipramine, or gabapentin, and for fibromyalgia after a failure of an antidepressant (amitriptyline, nortriptyline, imipramine, desipramine, or selective serotonin reuptake inhibitor - SSRI), cyclobenzaprine, tramadol, or gabapentin. The criteria for Topamax for migraine prevention encourage prior use of two other less-costly preventative medications, such as a beta-blocker, calcium channel blocker, TCA, divalproex or valproic acid, or gabapentin. Criteria for Lamictal, Lamictal ODT, Lamictal XR, and Trileptal for bipolar disorder encourage use of generic anticonvulsants indicated for bipolar disorder or lithium as first-line agents. The manual review process allows for individual review of claims for these agents that may meet the edit requirements when an epilepsy diagnosis or other anticonvulsant therapy is not apparent on electronic claim history, when Lyrica is prescribed for neuropathic pain or fibromyalgia, when Topamax is prescribed for migraine prophylaxis, or when Lamictal, Lamictal ODT, Lamictal XR, or Trileptal is prescribed for bipolar disorder. Use outside of Food and Drug Administration (FDA) labeling will be evaluated through the prior authorization process if the prescriber submits documentation supporting the target drug use for the patient's condition.

The intent of the Medical Diagnoses Option is to identify patients with certain medical diagnoses, to allow coverage of these brand anticonvulsants in members with a seizure disorder. Patients with one of these diagnoses are considered at higher risk for disease morbidity and mortality and will not be subject to this step therapy program. Medical claims data must be supplied to Prime in order to implement this option.

PROGRAM FUNCTIONALITY

Medical Diagnoses Option

The medical diagnoses included below will be used to identify patients for pre-approval of brand Keppra, Keppra XR, Lamictal, Lamictal ODT, Lamictal XR, Lyrica, Topamax, Trileptal, and Vimpat through the implementation process. The utilization management program for these anticonvulsants will not be required for them. Medical claims data supplied by the health plan will be used to identify plan members with the ICD-9 codes listed below:

Table 1: Medical Diagnoses Option Details

Event	ICD-9-CM Code*
Epilepsy	345, 345.X, 345.XX

*The Medical Diagnoses Criteria will approve ICD-9 codes of three or more digits as applicable to ensure that patients who have been assigned incomplete codes will be included.

These patients would be exempt from the prior authorization process for prescriptions for Keppra, Keppra XR, Lamictal, Lyrica, Topamax, Trileptal, and Vimpat.

Electronic Edits

The overall process for step therapy requires that another drug or drugs be tried in a specific previous time period before the claim drug. If the patient has met any of the requirements outlined below, the requested step therapy medication will be paid under the patient's current prescription benefit. If the patient has not met the requirements, the system will reject with the message indicating that prior authorization is necessary. The Prior Authorization (PA) Criteria for Approval would then be applied to requests submitted by the patient's practitioner for evaluation.

Table 2: Summary of Anticonvulsant Step Therapy

Targeted Agent(s)	Keppra, Keppra XR, Lamictal, Lamictal ODT, Lamictal XR, Lyrica, Topamax, Trileptal, Vimpat
Is auto-grandfathering implemented? (with look-back time frame)	Yes (90 days ^a)
Prerequisite Agent(s) – Epilepsy	Any anticonvulsant
Prerequisite Agent(s) – Neuropathic Pain	amitriptyline, nortriptyline, desipramine, imipramine, gabapentin
Prerequisite Agent(s) – Fibromyalgia	amitriptyline, nortriptyline, desipramine, imipramine, gabapentin, tramadol, cyclobenzaprine
Prerequisite Agent(s) – Bipolar Disorder	lithium
Number of prerequisites required	1
Prerequisite look-back time frame	90 days ^a
Age-related edit?	NA
Additional comments	<ol style="list-style-type: none"> 1. Anticonvulsant prerequisites include all anticonvulsants, brand and generic 2. Brand anticonvulsants will not be subject to step therapy if the Medical Diagnoses Option is implemented.

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

Table 3: Details of Anticonvulsant Step Therapy

Targeted Agents	GPIs (multisource code)	Prior Agents	GPIs (multisource code)	Look-back Time frames
ANY ONE of: Keppra, Keppra XR, Topamax, Vimpat	72600043*****, 72600075*****, 72600036*****, (M, N, or O)	For Prerequisites, ANY ONE of: any generic or brand anticonvulsant	72*****, 60100060*****, (M, N, O, or Y)	Prerequisite look-back time frame: 90 days ^a
		For auto-grandfathering, ANY ONE of: Keppra, Keppra XR, Topamax, Vimpat	72600043*****, 72600075*****, 72600036*****, (M, N, or O)	Auto-grandfathering look-back time frame: 90 days ^a
ANY ONE of: Lamictal, Lamictal ODT, Lamictal XR, Trileptal	72600040*****, 72600046*****, (M, N, or O)	For Prerequisites, ANY ONE of: any generic or brand anticonvulsant	72*****, 60100060*****, (M, N, O, or Y)	Prerequisite look-back time frame: 90 days ^a
		OR lithium	OR 5950*****, (M, N, O, or Y)	
		For auto-grandfathering, ANY ONE of: Lamictal, Lamictal ODT, Lamictal XR, Trileptal	72600040*****, 72600046*****, (M, N, or O)	Auto-grandfathering look-back time frame: 90 days ^a
ANY ONE of: Lyrica	72600057*****, (M, N, or O)	For Prerequisites, ANY ONE of: any generic or brand anticonvulsant	72*****, 60100060*****, (M, N, O, or Y)	Prerequisite look-back time frame: 90 days ^a
		OR gabapentin, amitriptyline, nortriptyline, desipramine, imipramine; tramadol, cyclobenzaprine	OR 7260003000*****, 58200010*****, 58200060*****, 58200050*****, 58200030*****, (M, N, O, or Y) 6510009510*****, 7510005010*****, (Y)	
		For auto-grandfathering, ANY ONE of: Lyrica	72600057*****, (M, N, or O)	Auto-grandfathering look-back time frame: 90 days ^a

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

Prior Authorization Criteria for Approval

The Prior Authorization (PA) Criteria for Approval provide a manual review process for claims that do not meet the electronic edit criteria and are not automatically paid. The criteria for approval through the PA process are identical to those set up in the electronic edit. The intent of the PA Criteria for Approval is to ensure that patients who have used a required prerequisite drug and patients with a documented seizure diagnosis are identified and approved, but that other indications for Keppra, Keppra XR, Lamictal, Lamictal ODT, Lamictal XR, Lyrica, Topamax, Trileptal, and Vimpat require additional evaluation. The PA criteria will allow for evaluation of Topamax for use in migraine prophylaxis, Lyrica for treatment of neuropathic pain or fibromyalgia, and Lamictal, Lamictal ODT, Lamictal XR, and Trileptal for bipolar disorder. Approval will be given to patients who have a history of trial and failure of a prerequisite agent outside of the 90-day look-back period or outside of the current benefit plan. Keppra, Keppra XR, Lamictal, Lamictal ODT, Lamictal XR, Lyrica, Topamax, Trileptal, or Vimpat may also be approved if the patient has tried a prerequisite agent and discontinued due to allergy, intolerance, or contraindication to the agent. The PA criteria will allow for continuation of therapy in individual patients already receiving Keppra, Keppra XR, Lamictal, Lamictal ODT, Lamictal XR, Lyrica, Topamax, Trileptal, and Vimpat. Use of these agents outside of FDA labeling will be evaluated if the prescriber submits documentation supporting the target drug use for the patient's condition.

Keppra, Keppra XR, Lamictal, Lamictal ODT, Lamictal XR, Lyrica, Topamax, Trileptal, and Vimpat will be approved indefinitely in patients with a documented diagnosis of epilepsy, due to their high risk for significant disease morbidity. Indefinite approvals granted through the Clinical Review PA process may be re-evaluated at some future time if new information changes selection criteria or safety issues develop that may place these patients at higher risk from drug therapy.

Lyrica (pregabalin)

Initial and Renewal Evaluation

1. Has the patient received and responded to Lyrica (pregabalin) in the past or is the patient currently receiving and responding to Lyrica (pregabalin) and switching could potentially cause harm or a health risk?
If yes, approve for 12 months. If no, continue to 2.
2. What is the patient's diagnosis?
 - a. Seizure disorder
 - b. Neuropathic pain
 - c. Fibromyalgia
 - d. OtherIf a, approve indefinitely. If b, continue to 3. If c, continue to 5. If d, continue to 7.
3. Has the patient tried and failed one of the following agents: amitriptyline, nortriptyline, desipramine, imipramine, or gabapentin?
If yes, approve for 12 months. If no, continue to 4.
4. Does the patient have an allergy, intolerance, or contraindication to one of the agents listed in question 3?
If yes, approve for 12 months. If no, continue to 6.
5. Has the patient tried and failed one of the following agents: an antidepressant (amitriptyline, nortriptyline, desipramine or imipramine or SSRI), cyclobenzaprine, gabapentin, or tramadol?
If yes, approve for 12 months. If no, continue to 6.
6. Does the patient have an allergy, intolerance, or contraindication to one of the agents listed in question 5?
If yes, approve for 12 months. If no, continue to 7.
7. Has the prescriber submitted and the pharmacist reviewed documentation in support of the requested therapeutic use for Lyrica (pregabalin) in this patient?
If yes, pharmacist must review and may approve for 12 months based on review of information provided.
If no, deny.

Topamax (topiramate)

Initial and Renewal Evaluation

1. Has the patient received and responded to Topamax (topiramate) in the past or is the patient currently receiving and responding to Topamax (topiramate) and switching could potentially cause harm or a health risk?
If yes, approve for 12 months. If no, continue to 2.
2. What is the patient's diagnosis:
 - a. Seizure disorder
 - b. Migraine headache
 - c. OtherIf a, approve indefinitely. If b, continue to 3. If c, continue to 5.
3. Has the patient tried and failed a minimum of two of the following agents for prophylaxis of migraine headache; 1) β -blockers, 2) tricyclic antidepressants, 3) divalproex or valproic acid 4) calcium channel blockers, or 5) gabapentin.
If yes, approve for 12 months. If no, continue to 4.
4. Does the patient have an allergy, intolerance, or contraindication to two or more of the above agents?
If yes, approve for 12 months. If no, continue to 5.
5. Has the prescriber submitted and the pharmacist reviewed documentation in support of the requested therapeutic use for Topamax (topiramate) in this patient?
If yes, pharmacist must review and may approve for 12 months based on review of information provided.
If no, deny.

Lamictal (lamotrigine), Lamictal ODT (lamotrigine orally disintegrating), Lamictal XR (lamotrigine extended-release), Trileptal (oxcarbazepine)

Initial and Renewal Evaluation

1. Has the patient received and responded to the requested agent in the past or is the patient currently receiving and responding to the requested agent and switching could potentially cause harm or a health risk?
If yes, approve for 12 months. If no, continue to 2.
2. What is the patient's diagnosis:
 - a. Seizure disorder
 - b. Bipolar disorder
 - c. OtherIf a, approve indefinitely. If b, continue to 3. If c, continue to 5.
3. Has the patient tried and failed a generic anticonvulsant indicated for bipolar disorder or lithium?
If yes, approve for 12 months. If no, continue to 4.
4. Does the patient have an allergy, intolerance, or contraindication to a generic anticonvulsant indicated for bipolar disorder or lithium?
If yes, approve for 12 months. If no, continue to 5.
5. Has the prescriber submitted and the pharmacist reviewed documentation in support of the requested therapeutic use for the requested agent in this patient?
If yes, pharmacist must review and may approve for 12 months based on review of information provided.
If no, deny.

Keppra (levetiracetam), Keppra XR (levetiracetam extended-release), Vimpat (lacosamide)

Initial and Renewal Evaluation

1. Has the patient received and responded to the requested agent in the past or is the patient currently receiving and responding to the requested agent and switching could potentially cause harm or a health risk?
If yes, approve for 12 months. If no, continue to 2.

2. What is the patient's diagnosis:
 - a. Seizure disorder
 - b. Other
 If a, approve indefinitely. If b, continue to 3.

3. Has the prescriber submitted and the pharmacist reviewed documentation in support of the requested therapeutic use for the requested agent in this patient?
If yes, pharmacist must review and may approve for 12 months based on review of information provided.
If no, deny.

CLINICAL RATIONALE

Seizure Disorders

The American Academy of Neurology (AAN) recommends patients with a newly diagnosed seizure disorder who require treatment be initiated on standard anticonvulsants such as carbamazepine, phenytoin, valproic acid/divalproex, phenobarbital, or one of the new anticonvulsants, gabapentin, lamotrigine, oxcarbazepine, or topiramate.¹⁴ The AAN has also published guidelines for use of the newer anticonvulsants in refractory epilepsy.¹⁵ These guidelines do not present a unifying definition of refractory epilepsy, but often patients were considered refractory or treatment resistant when they had failed three or more anticonvulsants.¹⁵ The following two tables (Table 4 and Table 5) summarize AAN guidelines for use of the newer anticonvulsants in new onset epilepsy and refractory epilepsy.^{14,15} Table 6 summarizes recommendations from Nadkarni, LaJoie, and Davinsky's 2005 review of current treatments for epilepsy.¹⁶ Neither the AAN guidelines from 2004 nor this 2005 review includes any recommendation for use of pregabalin or lacosamide.^{12,14-16} As seen below in Tables 4 and 5, for all types of seizures, there is at least one first line agent available as a generic product.

Table 4: American Academy of Neurology Evidence-Based Guidelines, New Onset Epilepsy¹⁴

Drug	Partial/Mixed (monotherapy)	Absence
Gabapentin	Yes*	No
Lamotrigine	Yes*	Yes*
Topiramate	Yes	No
Tiagabine	No	No
Oxcarbazepine	Yes	No
Levetiracetam	No	No
Zonisamide	No	No

*Not FDA-approved for this indication

Table 5: American Academy of Neurology Evidence-Based Guidelines, Refractory Epilepsy¹⁵

Drug	Partial, adjunctive, adult	Partial, monotherapy	Primary Generalized	Symptomatic Generalized	Pediatric Partial
Gabapentin	Yes	No	No	No	Yes
Lamotrigine	Yes	Yes	No	Yes	Yes
Topiramate	Yes	Yes*	Yes	Yes	Yes
Tiagabine	Yes	No	No	No	No
Oxcarbazepine	Yes	Yes	No	No	Yes
Levetiracetam	Yes	No	No	No	No
Zonisamide	Yes	No	No	No	No

*Not FDA-approved for this indication

Table 6: Recommendations for anticonvulsant therapy from Nadkarni, LaJoie, Davinsky¹⁶

	First Line drug	Second Line Drug	Third Line Drug
Primary Generalized Seizure:			
Absence	ethosuximide, valproic acid	lamotrigine	
Myoclonic	valproic acid	clonazepam, lamotrigine, primidone	levetiracetam, topiramate, zonisamide
Tonic-clonic	valproic acid, carbamazepine, oxcarbazepine, lamotrigine	phenobarbital, phenytoin, primidone, topiramate	levetiracetam
Epilepsy syndrome			
Childhood onset absence	ethosuximide	valproic acid, lamotrigine	
Adolescent onset absence	valproic acid	ethosuximide, lamotrigine	
Juvenile myoclonic	valproic acid	clonazepam, lamotrigine, levetiracetam, primidone, topiramate	felbamate
Lennox-Gastaut	valproic acid, lamotrigine	carbamazepine, oxcarbazepine, topiramate, zonisamide	clonazepam, felbamate, levetiracetam, phenobarbital
Partial			
Simple partial, complex partial, secondary generalized tonic-clonic	carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproic acid, zonisamide	phenobarbital, phenytoin, primidone, tiagabine	felbamate

Table 7: Recommendations from Treatment Guidelines from Medical Letter (2008)¹⁷

	Drugs of Choice	Alternative Agents
Primary Generalized Tonic-Clonic	valproate, lamotrigine, levetiracetam	carbamazepine, topiramate, zonisamide, oxcarbazepine, phenytoin
Partial, including Secondarily Generalized	carbamazepine, lamotrigine, oxcarbazepine, levetiracetam	topiramate, valproate, gabapentin, zonisamide, phenytoin pregabalin
Absence	ethosuximide, valproate	lamotrigine, clonazepam, zonisamide, levetiracetam
Atypical Absence, Myoclonic, Atonic	Valproate, lamotrigine, levetiracetam	topiramate, zonisamide, clonazepam, felbamate

Several guidelines from Europe¹⁸⁻²⁰ support the concept that optimal anticonvulsant therapy depends upon a variety of patient-specific factors including seizure diagnosis, age, body-weight, lifestyle, other medications, adverse-effect profiles of the anticonvulsants and other concomitant diseases. A 2006 review found topiramate to be the least well tolerated of the newer anticonvulsants used for focal-onset seizures.¹⁸ Based on published studies, the International League Against Epilepsy (ILAE) considers carbamazepine, phenytoin, and valproic acid to be efficacious first-line therapy for partial-onset seizures, with the newer agents (gabapentin, lamotrigine, oxcarbamazepine, topiramate, and vigabatrin) as possibly efficacious as initial monotherapy.¹⁹ For generalized seizures, carbamazepine, lamotrigine, oxcarbamazepine, phenobarbital, phenytoin, topiramate, and valproic acid are all considered possibly efficacious as initial monotherapy.¹⁹

Pregabalin is a structural analogue of gamma-aminobutyric acid (GABA), is similar to gabapentin, and has similar indications.⁵ Both are used to treat neuropathic pain and as adjunct therapy for partial onset seizures.⁵ Pregabalin has been shown to be more effective than placebo in patients with refractory partial seizures as an adjunctive treatment to currently taken anticonvulsants. (in three clinical trials there was a $\geq 50\%$ decrease in seizures compared to placebo with a -6% to -15% decrease in seizures). Since the duration of the trials was relatively short, the long term effectiveness of pregabalin remains unclear. Because pregabalin has been reported to cause euphoria (and may have abuse potential) it is designated as a schedule V controlled substance by the FDA.^{5,21,22}

The effectiveness of Keppra XR (levetiracetam extended-release or ER) as adjunctive therapy in patients with partial seizures was established in one multicenter, randomized double-blind, placebo-controlled clinical study across 7 countries in patients who had refractory partial onset seizures with or without secondary generalization.² Patients were taking a stable dose regimen of at least one and could take a maximum of three antiepileptic agents. The median percent reduction in weekly partial onset seizure frequency from baseline over the treatment period (12 weeks) was 46.1% in the Keppra XR 1000 mg group and 33.4% in the placebo group. The estimated percent reduction over placebo in weekly partial onset seizure frequency over the treatment period was 14.4%.²

FDA approval of lacosamide tablets was based on the results of three 12-week, randomized, double-blind, placebo-controlled, multicenter trials in patients with partial onset seizures with or without secondary generalization, who were not adequately controlled with 1 to 3 concomitant antiepileptic drugs. Study 1 was a published phase II trial comparing doses of lacosamide 200 mg, 400 mg, and 600 mg/day with placebo. Study 2 was a phase III trial comparing doses of lacosamide 400 and 600 mg/day with placebo and is only published in poster form. Study 3 is a phase III trial comparing doses of lacosamide 200 and 400 mg/day with placebo and is also published in poster form. The primary endpoint in these trials was reduction in 28 day seizure frequency (baseline to maintenance phase) as compared to the placebo group. A statistically significant effect was observed with lacosamide treatment at doses of 200 mg/day (Study 3), 400 mg/day (Studies 1, 2, and 3), and 600 mg/day (Studies 1 and 2). In clinical trials, the 600 mg daily dose was not more effective than the 400 mg daily dose, and was associated with a substantially higher rate of adverse reactions.^{8,23-25} Another published trial showed intravenous lacosamide had a similar safety and tolerability profile as the oral formulation when used as replacement therapy in patients with partial onset seizures who were taking oral lacosamide.²⁶

Neuropathic Pain

Pregabalin is also approved for treatment of pain associated with diabetic peripheral neuropathy (DPNP) and post-herpetic neuralgia (PHN). In clinical studies treatment with pregabalin was associated with $\geq 50\%$ reductions in patient reported pain scores compared with placebo in DPNP and PHN. There are no trials comparing pregabalin with other agents used to treat diabetic DPNP or PHN.^{21,22}

Table 8: Recommendations for Treatment of Neuropathic Pain^{27-41,84,85}

	First Line	Second Line	Third Line and Other
AAN ³² (2004)	amitriptyline, nortriptyline, desipramine, maprotiline, gabapentin, pregabalin, topical lidocaine, opioids		
Cochrane Reviews ³³⁻³⁵ (2004, 2005)	TCAs	gabapentin, other anticonvulsants	
ADA ²⁷⁻²⁹ (2005, 2009)	TCAs (amitriptyline, imipramine), duloxetine	gabapentin, pregabalin, lamotrigine, topiramate, carbamazepine	tramadol, oxycodone, capsaicin
Mayo Clinic ³¹ (2006)	TCAs (amitriptyline, desipramine), pregabalin, duloxetine, oxycodone CR	carbamazepine, gabapentin, lamotrigine, tramadol, venlafaxine ER	topical capsaicin cream, lidocaine patches
EFNS ⁴⁰ (2006)	TCAs, gabapentin, pregabalin	duloxetine, venlafaxine	

	First Line	Second Line	Third Line and Other
Maizels et al ^{84,85} (2005)	TCAs, gabapentin	bupropion, venlafaxine	opioids, tramadol
Gilron et al ^{84,85} (2006)	TCAs, gabapentin, pregabalin, SNRIs		
Cochrane Reviews ^{84,85} (2007)	TCAs, venlafaxine		
Dworkin ³⁶ (2007)	TCAs, SNRIs (venlafaxine, duloxetine), gabapentin, pregabalin	opioids, tramadol	carbamazepine, lamotrigine, valproic acid, oxcarbazepine, topiramate, bupropion, citalopram, paroxetine, mexiletine, capsaicin
AACE ³⁰ (2007)	duloxetine, pregabalin, TCAs, capsaicin, anticonvulsants		
Clinical Knowledge Summaries ³⁸ (2008)	TCAs (amitriptyline, nortriptyline, desipramine), gabapentin, pregabalin, lidocaine patch, tramadol, duloxetine, venlafaxine	paroxetine, citalopram, bupropion, lamotrigine, carbamazepine	
Wong et al ³⁹ (2007)	capsaicin and/or TCAs	sodium valproate, carbamazepine	pregabalin, gabapentin, duloxetine, opioids
IASP ^{84,85} (2007)	TCAs, SNRIs, gabapentin, pregabalin		
CPS ^{84,85} (2009)	TCAs, gabapentin, pregabalin	SNRIs, topical lidocaine	tramadol, opioids, lamotrigine, topiramate, valproic acid
NICE ⁴¹ (2009)	TCAs	duloxetine, gabapentin, pregabalin	opioids if others fail

Abbreviations: AAN – American Academy of Neurology; ADA – American Diabetes Association; AACE – American Association of Clinical Endocrinologists; CPS – Canadian Pain Society; EFNS – European Federation of Neurological Societies; IASP – International Association for the Study of Pain; NICE – National Institute for Health and Clinical Excellence; TCAs=tricyclic antidepressants, SNRI – serotonin-norepinephrine reuptake inhibitor,

Although carbamazepine is considered by some to have “stood the test of time” as far as effectiveness in neuropathic pain,³⁵ recent evaluations consider carbamazepine to be highly effective for trigeminal neuralgia but not necessarily beneficial for other types of neuropathic pain.^{33,36,40,42-45}

The manufacturer of lacosamide received non-approval for submissions in Europe and the U.S. for treatment of diabetic neuropathy. European reviews suggest that results of the phase III trials (unpublished) on lacosamide in treatment of diabetic neuropathy were difficult to interpret due to high patient withdrawal rates and high placebo responses. These questions regarding efficacy of lacosamide for diabetic neuropathy along with the drug’s cardiovascular and other safety concerns, especially in a diabetic population, should be considered.⁴⁶⁻⁴⁸ Lacosamide is new to the market (2009) and is not discussed in current guidelines on treatment of neuropathy. Because current data suggests there are questions regarding the benefits versus risks of using lacosamide in treatment of diabetic neuropathic pain, lacosamide will not be reviewed for treatment of neuropathic pain until more information becomes available.

Dworkin et al.³⁶ state that most randomized controlled trials of chronic neuropathic pain have examined only 2 pain syndromes, DPNP and PHN. These authors suggest that while the applicability of the results of clinical trials for one chronic neuropathic pain syndrome to others cannot be determined, most of the first-line therapies have been tested with multiple types of neuropathic pain and have shown similar results.³⁶

Fibromyalgia

Pregabalin is approved for management of fibromyalgia (FM), a disease characterized by widespread pain for longer than 3 months and bilateral sites of amplified tenderness.⁴⁹⁻⁵⁵ In most patients, FM is associated with fatigue, sleep dysfunction, stiffness, depression, anxiety, cognitive disturbance, or exercise intolerance. The etiology and pathophysiology of FM remain unclear; current hypotheses center on atypical sensory processing

in the CNS and dysfunction of skeletal muscle nociception and the hypothalamic-pituitary-adrenal axis.^{49,51,53} Randomized controlled trials are generally difficult due to factors such as a lack of understanding of the pathophysiology and a heterogeneous FM patient population.⁴⁹⁻⁵⁵

The efficacy of pregabalin for management of FM was shown in several clinical trials.⁵⁶⁻⁵⁸ Only one study has been published in full;⁵⁶ the two studies supporting the FDA approval (FREEDOM and RELIEF) are available as abstracts only.^{5,57,58} The information available shows that pregabalin doses of 300 mg, 450 mg, and 600 mg daily provide a significant improvement in pain score, with evidence of improvement as early as one week.⁵⁶⁻⁵⁸ In this pair of studies the reported response rate varied from about 30% to 60%; the placebo response occurring in these studies was also very high. There was no evidence of a greater effect on pain scores of the 600 mg daily dose than the 450 mg daily dose, but there was evidence of dose-dependent adverse reactions;^{5,58} in view of these dose-dependent adverse effects, treatment with doses above 450 mg per day are not recommended.⁵ The results of the RELIEF trial also showed an improvement in other symptoms of well-being as recorded by more global questionnaires.⁵⁸ Steven Galson, MD, MPH, director of the FDA's Center for Drug Evaluation and Research, cautioned "the drug was not a panacea because response to the drug was not universal."⁵⁹

Fibromyalgia is a disease characterized by widespread pain for longer than 3 months and bilateral sites of amplified tenderness.⁴⁹⁻⁶⁵ In most patients, FM is associated with fatigue, sleep dysfunction, stiffness, depression, anxiety, cognitive disturbance, or exercise intolerance. The etiology and pathophysiology of FM remain unclear; current hypotheses center on atypical sensory processing in the CNS and dysfunction of skeletal muscle nociception and the hypothalamic-pituitary-adrenal axis.^{49,51,53}

Randomized controlled trials are generally difficult due to factors such as a lack of understanding of the pathophysiology and a heterogeneous FM patient population.⁴⁹⁻⁶⁵ Clinical trials on FM have not accounted for the heterogeneity of the disease, and there is a lack of standardization (e.g., methods, outcome measures).⁶⁴

A variety of pharmacologic and nonpharmacologic treatments are offered to patients diagnosed with FM. To date no therapy has proven effective for the entire scope of symptoms and disabilities associated with FM.¹² Non-drug approaches (e.g., pool-based exercise, aerobics, strength training, physiotherapy) have been considered by some physicians to be among the most useful FM treatments. Certain treatments work in some patients, sometimes despite failure in clinical trials. Fibromyalgia treatment choices are made empirically, informed whenever possible by evidence.⁶⁴ Systematic reviews and guidelines on treatment of pain in FM show that there are several pharmacologic agents available generically for treatment of this condition.⁴⁹⁻⁶⁵

Because evidence for the long-term effects of drugs in treatment of FM are lacking, patients should be reevaluated at regular intervals considering the benefits versus side effects of the drug, and if benefits no longer exist, the drug should be discontinued.⁶¹

Guidelines on Management of Fibromyalgia

A systematic review (2009) compared recommendations from three evidence based guidelines published by professional organizations on the management of FM.⁶⁰

Table 9: APS, EULAR, and ASMS (Germany) Guideline Comparison⁶⁰

Comparison of the recommendations of the three guidelines (according to the APS guideline order of scientific evidence).

	American Pain Society		European League Against Rheumatism Level of Evidence		Association of the Scientific Medical Societies in Germany	
	Level of Evidence	Strength of recommendation	Level of Evidence	Strength of recommendation	Level of Evidence	Strength of recommendation
Aerobic exercise	I	A	IIb	C	Ia	A
Cognitive-behavioral therapy	I	A	IV	D	Ia	A
Amitriptyline	I	A	Ib	A	Ia	A
Cyclobenzaprine	I	A	*	*	Ia	C
Multicomponent therapy	I	A	*	*	Ia	A
Tramadol	II	B	Ib	A	IIb	C
Balneotherapy	II	B	IIa	B	IIb	B
Patient education alone	II	B	*	*	Ia	Not B
Hypnotherapy	II	B	*	*	IIb	B
Biofeedback	II	B	*	*	IIb	Not B
Massage therapy	II	B	*	*	IIb	B
Anticonvulsants	II	B	Ib	A	IIb	B
SSRI (Fluoxetine)	II	B	Ib	A	IIb	B
SNRI (Duloxetine)	II	B	Ib	A	IIb	B
Opioids	III	C	IV	Not D	IV	Not C
Acupuncture	II	C	*	*	Ia	Not A
Trigger point injection	III	C	*	*	IV	Not C

Not = Not recommended.

* No statement.

Table 10: Pharmacotherapy for Fibromyalgia

Reference	Effective Agents	Comments
Meta-analysis (JAMA, 2009) ⁶³	<ul style="list-style-type: none"> Effect sizes for pain reduction were large for TCAs, medium for MAOIs, and small for SSRIs and SNRIs. 	<ul style="list-style-type: none"> Included 18 RCTs, N=1427
Review Abeles ⁶⁴ (2008)	<ul style="list-style-type: none"> According to reviewer, for most patients the agent of first choice probably remains low dose amitriptyline or nortriptyline at bedtime. If these are not tolerated, low dose cyclobenzaprine at bedtime may be initiated; other muscle relaxants also might be efficacious. A patient with isolated generalized pain without other associated symptoms may respond to tramadol. Patients with depression may benefit from SSRIs or SNRIs. Patients who fail analgesics, muscle relaxants, or antidepressants may benefit from use of pregabalin or gabapentin. 	<ul style="list-style-type: none"> Several weeks of treatment may be required to derive benefit. Failure to respond to one agent indicates need for a trial/addition of another agent. Drugs may lose initial efficacy, requiring regular assessment and possible rotation of medications.
Guidelines EULAR ⁶⁵ (2008)	<ul style="list-style-type: none"> Tramadol, amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide, pirlindol, tropisetron, pramipexole, pregabalin, acetaminophen, weak opioids Amitriptyline had largest "effect size" for pain 1.033 (95% CI - 0.393, 2.458), NNH 45.56 (95% CI -36.06, 127.17) SSRI "effect size" 0.824 (95% CI -0.417, 2.064), NNH 8.25 (95% CI 5.8,10.7) SNRI "effect size" 0.341 (95% CI -0.644, 1.323), NNH 9.91 (95% CI 6.87,12.96) Tramadol "effect size" 0.657 (95% CI -0.276, 1.589), NNH 35 (only one study) 	<ul style="list-style-type: none"> Acetaminophen, weak opioids recommendation based mainly on expert opinion due to insufficient data
Review Chakrabarty ⁶² (2007)	<ul style="list-style-type: none"> Strong evidence: amitriptyline, cyclobenzaprine Moderate evidence: duloxetine, venlafaxine, fluoxetine ± TCA, pregabalin, tramadol ± acetaminophen No evidence: corticosteroids, melatonin, NSAIDs, opioids, thyroid hormone 	
Reviews Borg-Stein ⁵³ (2006), Mease ⁵⁴ (2005), Henningsen ⁵⁵ (2007)	<ul style="list-style-type: none"> TCAs, doxepin, SSRIs, venlafaxine, duloxetine, milnacipran gabapentin, pregabalin, opioids, tramadol, NSAIDs, sedative-hypnotics 	<ul style="list-style-type: none"> NSAIDs, sedative-hypnotics efficacy primarily in combination with other agents

Reference	Effective Agents	Comments
Reviews Goldenberg ⁵¹ , (2004), Rooks ⁵² (2007)	<ul style="list-style-type: none"> • First Line: amitriptyline, cyclobenzaprine • Second Line: SSRIs, duloxetine, pregabalin, venlafaxine, tramadol 	
Guidelines American Pain Society ⁵⁰ (2005)	<ul style="list-style-type: none"> • First line: TCAs (specifically, amitriptyline), and cyclobenzaprine) • Second Line: SSRIs, tramadol • Third Line: NSAIDs combined with TCAs or SSRIs, opioids 	

ACR=American College of Rheumatology; APS=American Pain Society; EULAR= European League Against Rheumatism, NSAIDs=nonsteroidal antiinflammatory agents, SNRIs=serotonin/norepinephrine reuptake inhibitors, SSRIs=selective serotonin reuptake inhibitors, TCA=tricyclic antidepressants, CI=confidence interval, NNH=number needed to harm, RCT=randomized controlled trial

Migraine Headache

Topiramate is indicated for the prophylactic treatment of migraine headache.⁶ Agents with medium to high efficacy, good strength of evidence, and only mild-to-moderate side effects (group 1) include amitriptyline, divalproex, propranolol, and timolol.⁶⁶⁻⁷⁰ Agents with less strength of evidence, lower efficacy, and mild to moderate side effects (group 2) include the β -blockers atenolol and metoprolol, the calcium channel blockers nimodipine and verapamil, fluoxetine, gabapentin, and NSAIDs.⁶⁶⁻⁷⁰ Guidelines from the National Institute for Clinical Excellence (NICE), suggest the evidence for NSAIDs is limited to cyclic prophylaxis in menses and that fluoxetine is not a first line prophylactic alternative.²⁰

A Cochrane review of anticonvulsant agents for migraine prophylaxis⁷¹ states that valproic acid/sodium valproate has proven efficacy for this use. This review suggested that gabapentin needed further evaluation and that topiramate had reasonable evidence to support its use.⁷¹ The EFNS guidelines from 2009⁷² support the use of β -blockers (propranolol and metoprolol), calcium channel blockers, and valproate as first-line prophylactic agents, as well as topiramate. Amitriptyline, naproxen, and bisoprolol are listed as second choices.⁷² The Institute for Clinical Systems Improvement (ICSI) guidelines for Diagnosis and Treatment of Headache from 2009⁷³ list all of the following as treatments for prophylaxis of migraine headaches: TCAs, beta blockers, divalproex, gabapentin, verapamil, topiramate.⁷³ Silverstein's 2009 review⁶⁹ lists the following as agents with high efficacy: propranolol, timolol, amitriptyline, valproate, topiramate, flunarizine; and the following to have lower efficacy: NSAIDs, atenolol, metoprolol, nadolol, verapamil, gabapentin.⁶⁹

Bipolar Disorder

Lamotrigine is indicated for maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy. The effectiveness of lamotrigine in the acute treatment of mood episodes has not been established.³ Oxcarbazepine as a mood stabilizing agent for bipolar disorder is supported as an accepted unlabeled use by the pharmaceutical compendia (American Hospital Formulary Service [AHFS], Clinical Pharmacology, Micromedex).⁹⁻¹¹ Guidelines usually list these two agents as second or third line agents.⁷⁴⁻⁷⁸ Increasing evidence suggests lamotrigine is beneficial for acute depressive episodes of bipolar disorder.⁷⁹

Table 11: Recommendations for Treatment – Acute Manic/Mixed Episodes⁷⁴⁻⁷⁷

	First Line	Second Line	Third Line	Other
APA	Li, VPA; add AAP if severe Alternatives: CBZ, OXC	Addition of another first line agent; addition of CBZ or OXC; add/ change AAP	ECT	
TMAP	Li, VPA, ARP, QTP, RIS, ZIP Alternatives: OLZ, CBZ	Li, VPA, AAP (Choose 2; not 2 AAPs; not ARP or CLOZ)	Li, VPA, AAPs, CBZ, OXC, TAP (Choose 2; not 2 AAPs; not CLOZ)	ECT or Add CLOZ or Li + [VPA or CBZ or OXC] + AAP
CANMAT	Li, VPA, OLZ, RIS, QTP, ARP, ZIP, (Li or VPA) + (RIS or OLZ or QTP)	CBZ, OXC, ECT, Li + VPA	HAL, CPZ, (Li or VPA) + HAL, Li + CBZ, CLOZ	
BAP	AAP, VPA, Li, CBZ	AAP + Li or VPA	CLOZ, ECT	

Abbreviations: APA=American Psychiatric Association, BAP=British Association for Psychopharmacology, CANMAT=Canadian Network for Mood and Anxiety Treatments, TMAP=Texas Medication Algorithm Project; AAP=atypical antipsychotic, ARP=aripiprazole, CBZ=carbamazepine, CLOZ=clozapine, ECT=electroconvulsive therapy, HAL=Haldol, Li=lithium, OLZ=olanzapine, OXC=oxcarbamazepine, QTP=quetiapine, RIS=risperidone, TAP=typical antipsychotic, VPA=valproate, ZIP=ziprasidone

Table 12: Recommendations for Treatment – Acute Depressive Episodes⁷⁴⁻⁷⁸

	First Line	Second Line	Third Line	Other
APA	Li, LTG Alternative: Li plus an antidepressant	Add LTG, BUP, PXT Alternative: add: SSRI, VEN, MAOI	Consider ECT	
TMAP	If on Li, increase Li to ≥ 0.8 mEq/L LTG Antimanic agent if history of recent or severe mania	QTP or OFC	Combination from Li, LTG, QTP, or OFC	[(Li, LTG, QTP, OFC, VPA, or CBZ) + (SSRI, BUP, or VEN)] or ECT; TCA, OXC, MAOIs, other AAPs or combos, pramipexole,
CANMAT	Li, LTG, (Li or VPA) + SSRI, OLZ + SSRI, Li + VPA, (Li or VPA) + BUP, QTP	QTP + SSRI, (Li or VPA) + LTG	CBZ, OLZ, VPA, Li + CBZ, (Li or VPA) + VEN, Li + MAOI, Li + pramipexole, ECT, (Li or VPA or AAP) + TCA, (Li or VPA or CBZ) + SSRI + LTG, adjunct TOP	
International Consensus Group	Li, LTG, QTP	OLZ, OFC; Add QTP, LTG,	VPA, CBZ, fluoxetine; Add BUP, modafinil, sertraline pramipexole	little evidence to support antidepressant monotherapy
BAP	QTP, LTG SSRI or antimanic agent if history mania	AAP if psychotic symptoms; consider ECT		Li, VPA if less severe symptoms

Table 13: Recommendations for Treatment – Maintenance⁷⁴⁻⁷⁷

	First Line	Second Line	Third Line	Other
APA	Li, VPA	LTG, CBZ, OXC		
TMAP– Manic/mixed episode	Li, VPA, LTG Alternative: OLZ	ARP	CBZ, CLOZ	QTP, RIS, ZIP, TAP, OXC, ECT
TMAP - Depressive episode	LTG, LTG + antimanic agent IF recent manic episode	Li	antimanic and antidepressant effective in the past, OFC	VPZ, CBZ, ARP, CLOZ, OLZ, QTP, RIS, ZIP, TAP, OXC, ECT
CANMAT	Li, LTG (lamotrigine mainly for those with mild manias), VPA, OLZ	CBZ, Li + VPA, Li + CBZ, (Li or VAP) + OLZ, ARP, RIS, QTP, ZIP, OFC, Li + (RIS or QTP), Li + (LTG or SSRI or BUP)	Adjunctive phenytoin, CLOZ, ECT, TOP, OXC, TOP, GAB	
CANMAT – with rapid cycling	Li, VPA	Li + VPA, Li + CBZ, (Li or VPA) + LTG, OLZ	(Li or VPA) + TOP, QTP, RIS, CLOZ, OXC	
BAP – mania predominant	Li	ARP, QTP, VPA, OLZ, CBZ, LTG	Combination therapy	CLOZ for refractory patients
BAP – depression predominant	QTP, LTG	Li	Combination therapy	CLOZ for refractory patients

Abbreviations: APA=American Psychiatric Association, BAP=British Association for Psychopharmacology, CANMAT=Canadian Network for Mood and Anxiety Treatments, TMAP=Texas Medication Algorithm Project; AAP=atypical antipsychotic, ARP=aripiprazole, BUP=bupropion, CBZ=carbamazepine, CLOZ=clozapine, ECT=electroconvulsive therapy, GAB=gabapentin, Li=lithium, LTG=lamotrigine, MAOI=monoamine oxidase inhibitor, OFC=olanzapine/fluoxetine combination, OLZ=olanzapine, OXC=oxcarbazepine, PXT=paroxetine, QTP=quetiapine, RIS=risperidone, SSRI=selective serotonin reuptake inhibitor, TAP=typical antipsychotic, TCA=tricyclic antidepressant, TOP=topiramate, VEN=venlafaxine, VPA=valproate, ZIP=ziprasidone.

The following medications have evidence supporting their use in bipolar disorder from clinical studies published after the publication of the American Psychiatric Association (APA) Treatment Recommendations for Patients with Bipolar Disorder in 2002.⁷⁹

Table 14: Additional Notes, Beneficial Agents, Guideline Watch (2005)⁷⁹

Acute Manic or Mixed	Acute Depressive	Maintenance
AAPs – OLZ (mono or adjunct), RIS (mono or adjunct), ZIP mono, ARP mono, QTP mono	OLZ or OFC – combination is superior QTP mono VEN or PXT – both effective	LTG vs Li – Li prevents manic or mixed; LTG prevent depress, manic, mixed OLZ = VPA OLZ superior to Li
CBZ ER	LTG	LI, CBZ, or VPA w/ OLZ beneficial

Abbreviations: AAP=atypical antipsychotic, ARP=aripiprazole, CBZ=carbamazepine, ER=extended release, Li=lithium, LTG=lamotrigine, OLZ=olanzapine, OFC=olanzapine/fluoxetine combination, QTP=quetiapine, PXT=paroxetine, RIS=risperidone, VPA=valproate, VEN=venlafaxine, ZIP=ziprasidone.

Other

Reviewers have identified six studies of topiramate for weight loss; however, all but one are available only as abstracts.⁸⁰⁻⁸² Guidelines for pharmacologic and surgical management of obesity from the American College of Physicians concluded that recommendations on use of topiramate for weight loss could not be made on the basis of one published study.⁸⁰ The PA Criteria for Approval will not approve topiramate for weight loss.

For Topamax, adverse events, in particular, the development of seriously decreased serum bicarbonate levels in some patients, and nephrolithiasis, ataxia, oligohidrosis, and ocular syndromes are of concern in therapies where patient benefits have not been clearly demonstrated in studies.⁶ Lamictal prescribing information includes a black box warning about the risk of serious rashes requiring hospitalization. There are suggestions that the risk of rash may be increased by coadministration of lamotrigine with valproate, exceeding the recommended initial dose of lamotrigine, or exceeding the recommended dose escalation for lamotrigine; however, cases have been reported in the absence of these factors³

Vimpat prescribing information recommends that caution be used in patients with known cardiac conduction problems, myocardial ischemia, or congestive heart failure due to potential for PR interval prolongation. Lacosamide may predispose patients to atrial arrhythmia, especially in patients with diabetic neuropathy and/or cardiovascular disease. The drug has also rarely caused multiorgan hypersensitivity reactions.⁸ Clinical studies suggest lacosamide may have abuse potential and the FDA is considering its schedule as a controlled substance.⁸³ These safety issues are a concern if lacosamide is considered for treatment of off-label conditions where patient benefits have not been clearly demonstrated (e.g., diabetic neuropathy, or other non-epilepsy conditions).

FDA-APPROVED INDICATIONS ¹⁻¹³

Table 15: FDA-Labeled and Accepted Unlabeled Indications

	Partial Seizures	Generalized Seizures	Other Seizure Indications	FDA-Labeled Non-seizure Indications	Accepted Unlabeled Uses (AHFS, Clinical Pharmacology, Micromedex)
Lamotrigine	X	X	Lennox-Gastaut	Bipolar disorder	
Lamotrigine ER	X				
Levetiracetam	X	X	Myoclonic		
Levetiracetam ER	X				
Oxcarbazepine	X				Bipolar disorder
Pregabalin	X			Neuropathic pain assoc with diabetic peripheral neuropathy Post-herpetic neuralgia Fibromyalgia	
Topiramate	X	X	Lennox-Gastaut	Migraine prevention	
Lacosamide	X				

FDA = Food and Drug Administration; AHFS = American Hospital Formulary Service

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84. Prime Therapeutics Formulary Chapter 9.2E: Antidepressants: Miscellaneous. September 2008.
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Original Prime Standard (Topamax and Zonegran) approved by UM Committee 02/2005
 Prime Standard 06/05 (Gabitril, Topamax, Zonegran)
 Prime Standard criteria approved by External UM Committee 08/2005
 Client Specific Criteria (automatic approval if previous history of selected agents) approved by client 11/2005
 Annual Review Prime Standard criteria with changes approved by External UM Committee 08/2006
 Client Specific Annual Review Client Specific Criteria approved by HCSC Corporate Clinical Committee 11/2006
 Annual Review Prime Standard criteria with changes approved by External UM Committee 05/2007
 Mid-year Review Prime Standard criteria with changes, addition of Lyrica fibromyalgia indication, approved by External UM Committee 08/2007
 Client Specific Annual Review Client Specific Criteria approved by HCSC Corporate Clinical Committee 09/2007
 Annual Review Prime Standard criteria with changes approved by P&T UM Committee 08/2008
 Mid-year Review Prime Standard criteria with addition of Keppra XR and generic levetiracetam approved by P&T UM Committee 11/2008
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